

WHAT IS CLAIMED IS:

1. A method for producing a subunit peptide originating from an oligomeric protein having disulfide bonds within a subunit and between subunits, which comprises the following steps:

(a) a step of refolding the subunit peptide by denaturing the oligomeric protein or its subunit peptide in a solution with a protein-denaturing agent and removing the denaturing agent from the solution in the presence of polyoxyalkyl polyether having a functional group that reacts with a thiol group; and

(b) a step of isolating the subunit peptide bonded to the polyoxyalkyl polyether from the solution.

2. The method according to Claim 1, wherein the subunit peptide isolated in step (b) has decreased antigenicity.

3. The method according to Claim 1, wherein the oligomeric protein is a dimer.

4. The method according to Claim 1, wherein the polyoxyalkyl polyether having the functional group that reacts with the thiol group is polyethylene glycol having a maleimide group.

5. The method according to Claim 1, wherein the subunit peptide originating from the oligomeric protein is a recombinant protein.

6. The method according to Claim 1, wherein the oligomeric protein or its subunit peptide is denatured under reducing conditions.

7. The method according to Claim 1, wherein a physiological activity of the oligomeric protein arises from a subunit peptide constituting the oligomeric protein, and the subunit peptide bonded to polyoxyalkyl polyether has the physiological activity.

8. The method according to Claim 1, wherein the subunit peptide bonded to polyoxyalkyl polyether has an activity of inhibiting a physiological activity of the oligomeric protein.

9. The method according to Claim 1, wherein the polyoxyalkyl polyether is bonded to a cysteine residue that is originally involved in formation of a disulfide bond between subunits in the oligomeric protein, among cysteine residues in the subunit peptide.

10. The method according to Claim 1, wherein the subunit peptide bonded to polyoxyalkyl polyether has a disulfide bond identical to a disulfide bond within the subunit in the oligomeric protein.

11. A subunit peptide originating from an oligomeric protein having disulfide bonds within a

subunit and between subunits, wherein

polyoxyalkyl polyether is bonded to a cysteine residue that is originally involved in formation of a disulfide bond between subunits of the oligomeric protein, among cysteine residues in the subunit peptide, and the subunit peptide has decreased antigenicity.

12. The subunit peptide according to Claim 11, wherein the oligomeric protein is a dimer peptide that originates from snake venom and has an activity of inhibiting binding of a von Willebrand factor to a platelet.

13. The subunit peptide according to Claim 12, wherein the snake venom is snake venom of *Crotalus horridus horridus*.

14. The subunit peptide according to Claim 12, which exhibits an antithrombotic activity.

15. The subunit peptide according to Claim 14, which is a peptide having the amino acid sequence shown in SEQ ID NO: 1 and having polyoxyalkyl polyether bonded to the cysteine residue of amino acid number 81 in the amino acid sequence, or a derivative thereof.

DISCLOSURE OF THE INVENTION

It is provided a method for producing a subunit peptide originating from an oligomeric protein having disulfide bonds within a subunit and between subunits. The method comprises producing a subunit originating from an oligomeric protein having disulfide bonds within a subunit and between subunits by the following steps:

(a) a step of refolding the subunit by denaturing the oligomeric protein or its subunit in a solution with a protein-denaturing agent and removing the denaturing agent from the solution in the presence of polyoxyalkyl polyether having a functional group that reacts with a thiol group; and

(b) a step of isolating the subunit bonded to the polyoxyalkyl polyether from the solution.